D3 sub E3 add 52-27.

A method according to claim 18 wherein the mutation in Rad51 affects interaction with p53.--

add E4

REMARKS

Claims 18, 19, and 21 are pending. Claims 22-27 are newly added. Applicants understand that the Amendment of November 30, 1999 was not entered. Applicants submit the amendment did not raise new issues and should have been entered and request reconsideration. In the meantime, Applicants have amended the claims herein as if the amendment was not entered. An appendix of the pending claims is attached for the Examiner's convenience.

Support for the amendments to Claims 18 and 19 is found throughout the specification, including on page 10, lines 17 and 20. Support for the amendment to Claim 21 is also found throughout the specification, including on page 16, lines 26-29. Support for new claims 22-23 is found throughout the specification, including page 33, lines 4-20 Support for new claims 24-25 is found at least on page 38, line 22. Support for new claims 26-27 is found at least on pages 16-17.

<u>The Rejections Under 35 U.S.C. Section 112, First Paragraph</u>

Claim 21 is rejected under 35 U.S.C. Section 112, first paragraph, as "not described in the specification in such a way as to enable one skilled in the art.....to make and/or use the invention". More particularly, the Office Action states that "neither the specification nor the prior art shows any disease that correlates with an aberrant Rad 51 gene". Applicants respectfully traverse.

Applicants submit the declaration of Dr. Gurucharan Reddy (enclosed herein as Exhibit A) as support for the correlation between aberrant Rad 51 and disease states. Dr. Reddy, as evidenced by his curriculum vitae, (attached as part of Exhibit A) has been an author on more than 20 scientific papers and review articles addressing the role of Rad51 in recombination and in DNA double-stranded break repair. Additionally, Dr. Reddy is familiar with normal and aberrant expression patterns of Rad51 in human tumor cell lines.

Based on his knowledge as a skilled artisan and the disclosure of the present application, it is Dr. Reddy's opinion that:

> aberrant Rad51 genes would cause changes in the biological function of Rad51, such as altered nucleic acid binding, filament formation, DNA pairing (i.e. D-loop formation), strand exchange, strand annealing or recombinagenicity. See paragraph 7 of Exhibit A.

It is further his opinion "that changes in the biological function of Rad51 would be correlated with a disease state." See paragraph 7 of Exhibit A.

Additional support can be found in the specification. For example, support for the correlation between nucleotide excision repair defective cells such as those in individuals suffering from the recessive heredity disorder Xeroderma pigmentosum (XP) is shown in Example 2, including on page 38, line 22. Support for the correlation between aberrant Rad 51 and cancer is shown on page 33.

Provided with the specific examples in the specification, the skilled artisan would find a correlation between disease states and aberrant Rad51. Thus, the skilled artisan would find the assertions made by Applicants reasonable, and would expect to be able to practice the claimed invention. Applicants, therefore, submit that Claim 21 is enabled and request that the rejection be withdrawn.

<u>The Rejections Under 35 U.S.C. Section 102</u>

Claims 18 and 19 are rejected under 35 U.S.C. Section 102(b) as anticipated by Ogawa, et al., RecA-like Recombination Proteins in Eukaryotes: Functions and Structures of RAD51 genes, Cold Harbor Symposium on Quantitative Biology, vol. 43, pages 567-576 (1993) (Ogawa). Applicants respectfully traverse.

To anticipate, each and every element must be disclosed. Ogawa does not disclose a method for determining whether a mammalian cell contains a mutant Rad51 gene. Moreover, Ogawa does not disclose a method for identifying Rad51 genotypes of human individuals. Therefore, Ogawa does not disclose each element of the claimed invention. Since Ogawa does not anticipate the claimed invention, Applicants request that the rejection be withdrawn.

Applicants submit that all the claims are in condition for allowance and an early notification of such is solicited.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON HERBERT, LLP

Dolly A. Vance
Reg. No. 39,054

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Telephone: (415) 781-1989
Date: 3-30-00

APPENDIX:

18. (Twice Amended) A method of identifying[determining whether] a mammalian cell [contains]containing a mutant Rad51 gene comprising determining the sequence of all or part of an endogenous Rad51 gene of a mammalian cell and comparing said sequence to a known mammalian Rad51 gene.

19. (Thrice Amended) A method of identifying a[the] Rad51 genotype of [an] a human individual comprising determining all or part of the sequence of at least one Rad51 gene of said individual and comparing said sequence to a known human Rad51 gene.

21. (Twice Amended) A method according to claim 19 [20] wherein a difference in the sequence between the Rad51 gene of said individual and said known Rad51 gene is indicative of a disease state or a propensity for a disease state, and wherein said difference in the sequence of the Rad51 gene in the individual results in aberrant Rad51.

22. A method according to claim 21 wherein said disease state is cancer.

23. A method according to claim 22 wherein said cancer is breast cancer.

24. A method according to claim 21 wherein said disease state is Xeroderma pigmentosum Type A.

25. A method according to claim 21 wherein said disease state is Xeroderma pigmentosum Type F.

26. A method according to claim 18 wherein the mutation in Rad51 affects biological activity and wherein said biological activity is selected from the group consisting of nucleic acid binding, filament formation, DNA pairing (i.e. D-loop formation), strand exchange, strand annealing, formation of foci and recombinagenicity.

27. A method according to claim 18 wherein the mutation in Rad51 affects interaction with p53.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner:	J. Brusca, Ph.D.
HAAF, et al.	)	Group Art Unit:	1636
Serial No.: 09/182,102	)		
Filed: 27 October 1998	)		
For: METHODS AND COMPOSITIONS UTILIZING RAD 51	)		

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Gurucharan Reddy, do hereby declare as follows:

1. I received a Ph.D. degree in Biochemistry in 1990 from the University of Poona in Poona, India. I have worked at Pangene Corporation for more than 3.5 years in the areas of DNA repair and recombination. My current title is Program Director in the Department of Oncology. Attached to this Declaration as Exhibit A is a copy of my curriculum vitae and a list of publications. I have authored and co-authored more than 20 scientific papers and review articles and authored more than 15 abstracts (not attached) presented at scientific meetings as lectures or posters.

APPLICANT'S EXHIBIT A

2. As evidenced from my curriculum vitae and publications, I have carried out and have been involved in research addressing the role of Rad51 in recombination and in DNA double-stranded break repair. Additionally, I am familiar with the state of the art regarding the detection of Rad51 foci in mammalian and yeast cells. Furthermore, I am familiar with normal and aberrant expression patterns of Rad51 in human tumor cell lines.

3. I have read and I understand the above-identified patent application of which I am a co-inventor and the Office Action mailed August 31, 1999. In the Office Action, it is stated that there is no guidance in this specification or prior art as to which Rad51 mutations are associated with disease. My opinions herein are based on my knowledge as a skilled artisan and the disclosure of the above identified patent application.

4. In my opinion, I would expect to see an aberrant distribution of Rad51 foci in individuals at risk for a disease state which results in aberrant Rad51 distribution. In my opinion, aberrant distribution of Rad51 foci is easily detectable as indicated in the application. Therefore, individuals at risk for disease states which result in aberrant Rad51 distribution can be diagnosed as such. For example, I would expect to see aberrant Rad51 foci in cells from individuals at risk for all types of cancer, in cells from individuals at risk for diseases caused by defective nucleotide repair and in cells from individuals at risk for diseases associated with cellular stress. In addition, apoptotic cells or cells under stress associated with nucleic acid modification can be identified by determining the distribution of Rad51 foci in affected and non-affected cells.

5. With regard to cancer, it is my opinion that aberrant Rad51 foci would be observed in cells obtained from individuals at risk for the following cancers: leukemia, chronic myeloid leukemia, acute myeloid leukemia, T-cell leukemia, cervical, ovarian, breast, testicular, colon, rectum, melanoma, oral cavity, and glioblastoma. In addition, it is

my opinion that the results obtained with the ovarian cancer line Hey in the application were erroneous.

6. It is also my opinion that ample examples of diagnosing disease states and the results of such diagnoses are provided in the application. For example, data is shown for cancer, XP-A and XP-F.

7. It is my opinion, that aberrant Rad51 genes would cause changes in the biological function of Rad51, such as altered nucleic acid binding, filament formation, DNA pairing (i.e. D-loop formation), strand exchange, strand annealing or recombinagenicity. It is my opinion that changes in the biological function of Rad51 would be correlated with a disease state.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful, false statements may jeopardize the validity/enforceability of the application or any patent issued thereon.

Date: 3/29/00

Gurucharan Reddy

Guru Reddy, Ph.D.

1405 Marshall Street, #510, Redwood City, CA 94063 Phone: 650-599-9439

PROFESSIONAL EXPERIENCE

PANGENE CORPORATION, Mountain View, CA. September 1996-Present
Senior Scientist & Program Director

- Identified Rad51 as a novel cancer drug target. Formed and directed a cancer group for the development of anticancer Rad51 inhibitor drugs.
- Set up in-house and external collaborative research projects to evaluate the therapeutic and diagnostic potential of Rad51.
- Worked closely with the scientists and patent lawyers to file patents to protect the cancer program. Filed several patents from the data generated at Pangene.
- Identified, evaluated and in-licensed patents from external sources to complement and extend our program.
- Worked closely with the President and CEO in strategic planning, development, presentation and out-licensing the company platform technology.
- Worked extensively in setting up strategic alliances with pharmaceutical companies for Rad51 and Rad52 drug targets.
- Highly experienced in technology evaluation, in-licensing and out-licensing activities.
- Worked closely with patent and legal attorneys in structuring and negotiating licensing deals.
- Highly experienced in writing research and business proposals to corporate partners and government sources.

YALE UNIVERSITY, New Haven, CT February 1991- August 1996
Associate Research Scientist

Worked with Prof. Charles Radding on the biochemistry of homologous recombination for about 5 years and obtained extensive experience in both prokaryotic and eukaryotic recombination enzymes such as RecA protein, beta protein of phage lambda, human Rad51 and Rad52 proteins and published 12 papers in respected journals like PNAS, TIBS, Biochemistry, JMB etc. I prepared the first antibody probes to human Rad51 and used them in a collaborative study with David Ward laboratory to demonstrate that Rad51 is directly involved in meiotic recombination, class switch recombination and DNA repair. We demonstrated that Rad51 is induced in response to DNA damage either by radiation or by DNA damaging chemicals. In addition we discovered that Rad51 is over-expressed in a number of tumor tissues and cell lines. Based on this work we filed two patents on Rad51 and Rad52 for therapeutic and diagnostic applications.

UMDNJ, New Jersey Medical School, Newark, NJ, Feb. 1990-Feb. 1991
Post-Doctoral Fellow

Worked with Prof. Mukund Modak on the active site characterization of MuLV reverse transcriptase for about an year. I characterized the substrate binding sites of MuLV reverse transcriptase and published the results in the journal Biochemistry

Education

Ph.D. in Biochemistry, National Chemical Laboratory, Poona University, Poona, India. 1985-1990. Worked on the purification, immobilization and active site characterization of S1 nuclease from *A. oryzae* and published 8 papers in internationally reputed journals.

M.Sc. (Biochemistry), University of Hyderabad, Hyderabad, India. 1982-1984

B.Sc. (Hons) (Biochemistry and Microbiology), Osmania University, Hyderabad, India. 1979-1982

AWARDS

Junior and Senior Research Fellowships awarded by the Council of Scientific and Industrial Research (CSIR), India. 1985-1990

PUBLICATIONS

1. L. G. Reddy and V. Shankar. (1987) Immobilization of single-strand specific nuclease (S1 nuclease) from *A. oryzae*. *Appl. Biochem. Biotechnol.* 14, 231-240.

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3. L. G. Reddy and V. Shankar.(1989) Influence of lectin concentration on the catalytic properteis of S1 nuclease bound to concavalin A-Sepharose.*Appl. Biochem. Biotechnol.* 22, 79-94.

4. L. G. Reddy and V. Shankar. (1989) Preparation and properties of RNase T2 immobilized on Concavalin A-Sepharose. *Appl. Biochem. Biotechnol.* 22, 237-246.

5. G. Reddy., V. B. Nanduri., A. Basu and M. J. Modak. (1991) Ferrate oxidation of Murine Leukemia Virus Reverse Transcriptase: Identification of template-primer binding site. *Biochemistry* 30, 8195-8201.

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